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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/589,255	06/07/2000	Charles J. Link JR.	P04091US1	8671

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/589,255	LINK	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-27,29,31-33 and 35-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-27,29,31-33 and 35-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response received on 9/3/04 has been entered. Claims 19-27, 29, 31-33, and 35-39 are pending in the instant application. An action on the merits follows.

Those sections of Title 35, US code not included in this action can be found in the previous office action.

Claim Rejections - 35 USC § 102

The rejection of claims 19-27, 29, 31-33, and 35-39 under 35 U.S.C. 102(b) as being anticipated by Link et al. (1996) Human Gene Therapy, Vol. 7, 1161-1179, is withdrawn over claims 26-27, 29, 31, 35, and 39, and maintained over claims 19-25, 32-33 and 36-38. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that claims 19-25, and 32-33 have been amended to recite that the administration of the xenogeneic cells occurs "without the administration of gancyclovir", and that Link et al. teaches a method that involves the administration of gancyclovir following the administration of the xenogeneic VPCs. In response, please note that claims 32 has been amended to recite a method comprising delivering at or near a tumor xenogeneic cells that express alpha (1,3) galatosyl epitopes, "thereby causing a local hyperacute rejection response against said xenogeneic cells and a bystander immune reaction against the tumor in the absence

of ganciclovir". Contrary to applicant's interpretation of the amendment, the claims do not preclude subsequent administration of ganciclovir. The added claim limitation simply states that the hyperacute rejection response and bystander immune reaction occurs in the absence of gancyclovir. The method as amended therefore reads on the administration of the cells followed by a waiting period in which the hyperacute reaction occurs, followed by the administration of gancyclovir. Link et al. teaches just such a method. Thus, the amendment to claim 32 does not overcome the rejection of record over claim 32 and dependent claim 33. In regards to claims 19-25, claim 19 has been amended to recite a method comprising administering xenogeneic cells, "without administration of ganciclovir", thereby treating said tumor. Again, the added claim limitation does not preclude the subsequent administration of gancyclovir, the method simply states that the xenogeneic cells are administered without ganciclovir. Thus, the claims as amended continue to read on method where ganciclovir is administered subsequent to the administration of the cell. Again, Link et al. teaches just such as method where the cells are administered alone without ganciclovir. In addition, it is noted that claim 36 and thus dependent claims 37-38 have not been amended to recite that the method does not include the administration of ganciclovir. As such, applicant's arguments that the claim amendments overcome the rejection of record is not found persuasive.

The applicant further argues that the "bystander effect" taught by Link et al. is not the same as the "bystander immune response" recited in the claims, and the Link et al. further does not teach that the anti-tumor immune responses observed by Link et al. following the VPC administration is the result of anti-gal antibodies and complement killing of the tumor cells. In response, it is noted that the Link et al. reference was authored by the inventors of the instant

application and that the methods described by Link et al. use the exact same xenogeneic VPCs as the applicants and utilize the same method of administration. The applicant appears to be arguing that since the Link et al. reference did not recognize that hyperacute rejection can mediate tumor killing through complement, Link et al. cannot anticipate the instant claims. However, as stated in the previous office action, the ability of the murine VPCs to induce hyperacute rejection in humans is an inherent property due to the fact that murine cells naturally express alpha (1,3,) galactosyl epitopes and the fact that humans possess preformed anti-xenogeneic antibodies. Further, there is no requirement that Link et al. must recognize all the potential properties of the murine VPCs once they have been administered to the human. The applicant has not provided any evidence that the murine VPCs used by Link et al. are functionally different than those taught by applicants. Case law is clear that merely discovering and claiming a new benefit to an old process cannot render the process again patentable. See *In re Woodruff*, 919 F. 2d 1575, 1577-78, 16 USPQ2d 1934, 1936-37 (Fed.Cir. 1990); *In re Swinehart*, 439 F.2d 210, 213, 169 USPQ 226, 229 (CCPA 1971); and *Ex Parte Novitski*, 26 USPQ2d 1389, 1391 (Bd. Pat. App. & Int. 1993). Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. *In re Wiseman*, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979). Therefore, since Link et al. teaches the same method steps as those recited in the claims, using the same VPCs as disclosed by applicants, Link et al. anticipates the claims as written.

Thus, for the reasons discussed above and in previous office actions, applicant's arguments do no overcome the instant rejection. The rejection of record is therefore maintained.

The following new grounds of rejection applies to the claims as amended.

Claim Rejections - 35 USC § 112

Claims 19-27, 29, 31-33, and 35-39 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting the growth of a solid tumor in a human subject comprising administering at or near a solid tumor an effective amount of xenogeneic retroviral vector producer cells having alpha (1,3) galactosyl epitopes, wherein said amount activates a hyperacute rejection response against said xenogeneic cells and an innocent bystander immune response against tumors cell, thereby inhibiting the growth of the tumor in the human subject with or without the subsequent administration of gancyclovir, does not reasonably provide enablement for methods of treating non-solid tumors by administering xenogeneic cells or methods of treating solid tumors comprising administering xenogeneic cells which are not vector producing cells to any site in the subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The specification does not provide an enabling disclosure for methods of treating tumors comprising the administration of xenogeneic cells which are not vector producing cells to any site in a human subject. The claims as amended now recite methods for treating tumors in a human comprising administering an effective amount of xenogeneic cells having alpha (1,3,) galactosyl epitopes without the administration or subsequent administration of ganciclovir. The specification broadly discloses that cells expressing alpha (1,3) galactosyl epitopes can be

administered to a human in order to stimulate hyperacute rejection of the xenogeneic cells leading to an innocent bystander immune response against tumor cells present in the subject. While the specification speculates that any xenogeneic cell expressing alpha (1,3) galactosyl epitopes would be capable of use in the instant invention, the specific guidance provided by the specification, including the working examples, is solely directed to the administration of murine vector producing cells at or near the site of a solid tumor. The applicant's declaratory evidence provided in the declaration under 37 CFR 1.132 is also limited to methods of administering murine vector producing cells at or near the site of a solid tumor. It is further noted that all of the data provided in the specification and the declaration derive from experiments wherein the administration of the murine vector producing cells which contain retrovirus encoding HSV-TK is followed by the administration of ganciclovir. Although the applicant states that evidence of anti-tumor immune responses was detected prior to the gancyclovir administration, it is unclear what types of immune responses were responsible for the therapeutic effect. The murine VPCs used in these experiments express not only the alpha (1,3) galactosyl epitopes but also viral proteins from the retrovirus. At the time of filing, the art recognized that both xenogeneic antigens and viral proteins are capable of stimulating immune responses in humans. For instance, Long et al. reported that the administration of similar murine VPCs as used by applicants to human patients in multiple clinical trials resulted in detectable immune responses against the xenogeneic cells themselves and retroviral proteins such as p30 (Long et al. (1998) Human Gene Therapy, Vol. 9, 1165-1172). Since the VPCs produce retrovirus capable of infecting the neighboring tumor cells, it is unclear whether the anti-tumor responses observed are the result of anti-retroviral immune responses, hyperacute immune responses against the gal epitopes on the

murine VPCs leading to innocent bystander killing of the tumor cells, or a combination of the two. As such, the skilled artisan would not have been able to predict without undue experimentation whether the administration of murine cells or other xenogeneic cells expressing gal epitopes which are not vector producing cells would be capable of stimulating sufficient immune responses such that innocent bystander immune responses against the tumor would occur and would result in treatment of the tumor.

In addition, the specification clearly teaches that immune responses against the tumor are "innocent bystander immune responses". In other words, the disclosed methods do not generate specific anti-tumor immune responses, rather the immune responses generated against the xenogeneic antigens and/or retroviral antigens expressed by the xenogeneic cells are capable of non-specifically killing other cells in the vicinity of the xenogeneic cells. The specification does not provide any guidance or evidence that hyperacute immune responses are capable of killing tumors distal to the site of administration of the xenogeneic cells. Neither the art at the time of filing, nor the specification or declaration, provide any evidence that the administration of xenogeneic cells or xenogeneic VPCs results in systemic non-specific killing of cells, or the non-specific killing of any particular cells type distant from the site of xenogeneic cell administration. If such were the case, the numerous clinical trials in humans using xenogeneic cells and xenogeneic VPCs would have reported widespread tissue necrosis following xenogeneic cell administration. Instead, both the prior art and the specification agree that hyperacute immune responses are limited to the cells expressing the xenogeneic antigens with potential bystander damage to cells in the vicinity of xenogeneic cells. Therefore, in view of the nature of "innocent bystander" immune responses, the skilled artisan would have considered it unpredictable that the

administration of xenogeneic cells having gal epitopes to humans would result in any effect on tumor cells not in the immediate vicinity of the xenogeneic cells. Thus, it would have required undue experimentation to practice the instant invention by administering the xenogeneic cells in any location other than at or near a tumor.

Furthermore, because of the requirement that the xenogeneic cells be present near the tumor in order to generate bystander immune responses capable of treating the tumor, the skilled artisan would have considered it unpredictable that the administration of xenogeneic cells to any site in a human would be capable of treating a liquid tumor. Unlike solid tumors, liquid tumors such as leukemia are present in the circulation and are not limited to any specific location such that the xenogeneic cells could be administered at or near the tumor cells. Although systemic administration of the xenogeneic cells, for instance by intravenous administration, would place the cells into the bloodstream, it is unlikely that hyperacute immune responses stimulated against these cells would be capable of non-specifically killing tumor cells also present in the circulating blood due to the physical conditions present in the blood vessels, particularly the rate of blood flow. Thus, in view of the nature of liquid tumors, which circulate freely in the blood, and the nature of the "innocent bystander effect", it would have required undue experimentation to practice the invention as claimed for the treatment of tumors other than solid tumors.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be

reached Monday- Friday from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. For all official communications, the technology center fax number is (703) 872-9306. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE, PH.D
PRIMARY EXAMINER